ALTERNATIVE CELL DEATH PATHWAYS IN THE REGULATION OF IMMUNE RESPONSE

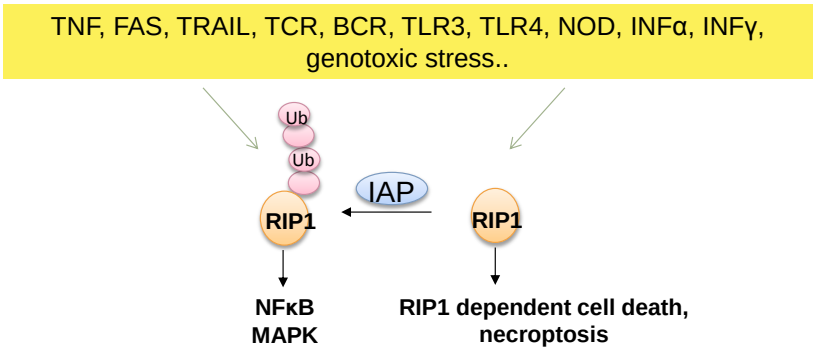
The balance of cell proliferation and cell death plays a crucial role in tissue development, maintenance of immune homeostasis, initiation of inflammatory diseases, generation of malignant tumors and degenerative disorders. In the past few years novel non-apoptotic cell death pathways have been discovered and classified. Tumor cells often have faulty apoptotic pathways and these defects not only support tumor growth, but also render tumor cells resistant to chemotherapy. The inactivation of apoptosis rationalizes the activation of non-apoptotic cell death pathways for therapeutical intervention, restoring the sensitivity of apoptosis- resistant tumors to cell death. Beside the intensity of cell death the immunological outcome of this process is of paramount importance .Dysregulation of the balance of tolerogen or inflammatory cell death processes contributes to a wide range of human diseases. Currently, the identification of molecular mechanisms operating in the course of alternative cell death pathways are just about emerging.

We study:

I. The molecular background of necroptosis

Necroptosis has been considered as a regulated cell death process, which induces the simultaneous activation of inflammation and adaptive immune responses. Necroptosis is a programmed rather than accidental cell death process, which utilizes a unique signalling pathway that requires the involvement of receptor interacting protein 1 **(**RIP1), RIP3 and MLKL. Currently, the necroptotic pathway is considered to act as a backup for apoptosis. The current explanations of the mechanisms, which may regulate the interplay of apoptosis and necroptosis rely on caspase-8-mediated cleavage of key components of necroptosis.

- We plan to investigate the key components of the necroptotic signaling pathway and the cross-regulation of apoptosis and necroptosis



Ubiquitination status of RIP determines the outcome of signaling

II. The role of apoptosis inhibitor proteins in the regulation of immune response

Apoptosis inhibitor proteins (IAPs) prevent unregulated induction of apoptotic cell death by binding to and inhibiting activated caspases, which are essential for apoptosis to occur. In addition to play a role in caspase inhibition IAPs also contribute to innate immunity at multiple levels. Through their ubiquitin ligase activity IAPs directly control the MAPK and NF-κB signaling pathways downstream of various TNF receptor family members and they function as direct regulators of signal transduction initiated by several PRRs and/or cytokines. RIP1 also contributes to RIP1-mediated cell death signaling. The poly-ubiquitinated status of RIPK1 supports cell activation and concomitantly prevents the generation of alternative cell death pathways, while deubiquitination is essential for switching to the RIP1-mediated cell death mode. Ubiquitination of RIP1 is cIAP-dependent, as depletion of cIAPs prevents RIP1 ubiquitination and also blocks several inflammatory signals, while in the mean time favours the induction of RIP1-mediated alternative cell death pathways.

- We plan to study how the expression level and activity of IAPs are regulated in various immune reactions